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Plasma Lipoprotein(a) and Its Relationship with Disease Activity in Patients with *Behçet*'s Disease

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Summary: *Behçet*'s disease is characterized by orogenital ulcerations and ocular lesions. Other features include arthritis, thrombophlebitis, neurological abnormalities and skin lesions. The disease is characterized by a relapsing inflammatory process of unknown aetiology. Lipoprotein(a) is an LDL-like particle with a large glycoprotein called apolipoprotein(a) attached to its apolipoprotein B moiety through one or more disulphide bonds. Apolipoprotein(a) is related to plasminogen from which the enzyme plasmin, that hydrolyses fibrin blood clots, is released by tissue plasminogen activators. The unique structural features of Lp(a) give it the potential for atherogenic and thrombogenic activities. In the present study 35% of patients with *Behçet*'s disease were shown to have higher Lp(a) concentrations than the cut-off point (0.30 g/l) for atherosclerosis. Plasma Lp(a) concentrations in the remission period were also found to be lower than during the active period in the same patients (23% decreased). Lp(a) showed significant correlations with acute phase reactants such as erythrocyte sedimentation rate, polymorphonuclear leukocytes and polymorphonuclear leukocyte elastase activity. Therefore, it was concluded that the fluctations of plasma Lp(a) levels with the activity of disease may be a contributing risk factor in the development of thrombogenic complications in patients with *Behçet*'s disease.

In conclusion, we suggest that plasma Lp(a) concentrations be determined for patients with *Behçet*'s disease, and that patients with high Lp(a) levels be kept under close controls especially during the active period of the disease, and taken into remission as soon as possible.

Introduction

Behçet's disease was discovered by Dr. *Hulusi Behçet* in 1937 and is characterized by oral and genital ulcers and eye inflammation (1). Other features include arthritis, thrombophlebitis, neurological abnormalities and skin lesions (2). The disease affects the arteries and veins. The predominant histopathological lesion is a vasculitis with the vessel walls and perivascular tissues infiltrated mainly by lymphocytes but also by monocytes, plasma cells and neutrophils (3, 4). Thrombosis is one of the vascular manifestations and is seen in about one third of the patients (5). The basis of thrombosis in the patients is unclear. One of the factors responsible for development of thrombotic events in *Behçet*'s disease is thought to be association of defective fibrinolysis (6). Many studies have indicated that reduced fibrinolysis may be related to decreased endothelial cell production of tissue plasminogen activator and increased concentration of tissue plasminogen activator inhibitor-1 in patients with *Behçet*'s disease (6, 7). The change of endothelial cell mediated production and release due to vasculitic damage is reported to be related to disease activity (3).

Lipoprotein(a) [Lp(a)] described by *Berg* in 1963 constitutes a newly recognized cardiovascular risk factor with implications in atherogenic and thrombogenic processes

(8). The protein moiety of human Lp(a) is composed of apolipoprotein B_{100} and the unique, highly glycosylated glycoprotein apolipoprotein(a), which is heterogeneous in size. The two protein moieties are linked by disulphide bridges. The apolipoprotein(a) gene is highly homologous to plasminogen and contains multiple repeats of a kringle 4 motif. Apolipoprotein(a) exhibits a striking size polymorphism, with the apolipoprotein(a) isoproteins ranging in size from M_r 420 000 to 840 000. Inherited in an autosomal codominant fashion, the apolipoprotein(a) isoprotein is an important factor in determining plasma Lp(a) concentration, with an inverse correlation between the size of the apolipoprotein(a) isoprotein and the plasma Lp(a) concentration (9, 10). Due to the striking similarity of apolipoprotein(a) to plasminogen, Lp(a) was suggested to act as an interloper in the fibrinolytic system by competing with plasminogen for its binding sites in a dose-dependent manner and inhibiting plasminogen activation (11, 12). Therefore, elevated plasma Lp(a) levels favour receptor occupancy by the lipoprotein particle and are associated with an increased thrombotic risk. It was reported that plasma Lp(a) levels are influenced by activity of diseases such as myocardial infarction, and by before and after surgical operation, but are hardly affected by diet, age, sex or treatment with lipid-lowering drugs (13–14).

In view of the above mentioned data, we have suggested that high Lp(a) levels in patients with *Behçet*'s disease may be a contributing risk factor for the development of thrombotic events (15). In the present study, we aimed to conform our previous data on the expanded patient group and to clarify the relationship of Lp(a) levels with the disease activity.

Materials and Methods

The study group included 45 patients with *Behçet*'s disease (male 24 and female 21) with a mean age of 30.8 (age range: 17–55) and 40 healthy volunteers (male 20 and female 20) with a mean age of 31.1 (age range: 17–52). The patient group had a mean body mass index (body weight in kg/squared height in m = kg/m^2 height) of 22.8 ± 5.1 (mean ± SD) which was similar to that of the control group of 23.4 ± 3.9. All the patients were diagnosed separately by the Internal Medicine, Dermatology and Ophthalmology Departments. The diagnosis of *Behçet*'s disease was made according to the criteria from the International Study Group for *Behçet*'s disease (16). The disease activity was evaluated by physical manifestations such as oral aphthous, genital ulcerations, uveitis and vasculitis and appropriate laboratory investigations such as erythrocyte sedimentation rate, polymorphonuclear leukocytes count, polymorphonuclear leukocyte elastase and α_2-globulins. Six of the patients had thrombotic complications such as superficial thrombophlebitis, which had superimposed segmental thrombosis areas, laying on the veins of lower extremity. At the time of the study, the patients were receiving neither steroids nor lipid-lowering drugs.

Blood samples of 2.5 ml were drawn in collection tubes with EDTA (1 g/l) anticoagulant and of 5 ml in tubes without anticoagulant in the morning by venipuncture after an overnight fast. Anticoagulated blood was divided into two aliquots. Polymorphonuclear leukocyte count, erythrocyte sedimentation rate were determined immediately in one aliquot. The second aliquot and blood sample without anticoagulant, that were allowed to clot for 1 h at room temperature, were centrifuged at 1500 *g* for 15 min immediately to obtain plasma or serum samples. The serum samples were divided into two aliquots. One was used for determinations of lipids, lipoproteins and protein electrophoresis. The other serum samples for Lp(a) measurements and plasma samples for polymorphonuclear leukocyte elastase measurement were stored at −70 °C until the time of analysis within 3 months.

Serum cholesterol was measured by a cholesterol oxidase enzymatic method, triacylglycerols by a glycerol oxidase enzymatic method, HDL-cholesterol by a cholesterol oxidase enzymatic method in supernatant after precipitation with phosphotungstic acid-$MgCl_2$ and apolipoprotein A-I and B by a turbidimetric immunoassay method [Sera-Pak Immuno Apo A I (Code no: 6821)/Apo B (Code no: 6822), Ames, Canada]. All determinations including immunoassays were carried out by autoanalyzer (Technicon Axon). LDL-cholesterol was calculated by *Friedewald* formula (17). Serum Lp(a) was measured using a commercial anti-apolipoprotein(a) polyclonal capture enzyme-linked immunosorbent assay called TintElize lipoprotein(a) (Catalog no: 610220; Biopool AB, Umea, Sweden) according to the instruction sheet of manufacturer. Using the above described method of analysis for Lp(a), intra-assay coefficients of variation of 5.6 and 6.1 percent were obtained at the 0.310 and 0.60 g/l of Lp(a) (n = 10), respectively.

Polymorphonuclear leukocyte elastase was determined by a rapid homogenous immunoactivation (IMAC) assay, using monospecific polyclonal antibodies directed solely against polymorphonuclear leukocyte elastase (18). Test kit was purchased from Merck (D-64271 Darmstadt) (cat no.: 113322). Within-run CV% at 52 µg/l (control plasma) was estimated as 5.2 (n = 10). Polymorphonuclear leukocytes (granulocytes) were counted by an automated blood counter (MaxM, Coulter), erythrocyte sedimentation rate was determined by classical *Westergren* method, serum α_2-globulins by protein electrophoresis (Helena Lab).

Plasma concentration of the lipids, lipoproteins and acute phase reactants in the patients and in the controls were compared by the *Mann-Whitney* U test or *Student*'s t test. Relationships among variables have been assessed by means of *Pearson*'s product-moment (r) correlation coefficients. *Wilcoxon* test was used to compare the results in the active and inactive periods of the disease.

Results

The distribution and concentrations of serum Lp(a) in patients with *Behçet*'s disease and in control subjects are shown in table 1 and figure 1. Plasma Lp(a) concentrations in the patients were significantly higher than those of control group ($p < 0.05$). Plasma Lp(a) concentrations in patients with *Behçet*'s disease were found to be approximately equal to the cut-off point (0.300 g/l) for a two-fold risk for atherothrombosis (19) and higher than the cut-off point (0.18 g/l) for a twenty-one-fold risk of cerebrovascular disease (20). According to figure 1, Lp(a) levels of sixteen patients (35%) and six control subjects (15%) were found to be higher than the cut-off point for atherosclerosis. Lp(a) levels were significantly correlated with apolipoprotein B, polymorphonuclear leukocyte and polymorphonuclear leukocyte elastase levels ($r = 0.52$, $p < 0.01$; $r = 0.39$, $p < 0.05$; $r = 0.36$, $p < 0.05$; respectively). The mean serum apolipoprotein A-I level was significantly lower than in the controls

Tab. 1 Lipids, lipoproteins and some acute phase reactants in patients with *Behçet*'s disease and in control group.

Analytes	Controls (n = 40) (mean ± SD)	Patients (n = 45) (mean ± SD)	p
Lipoprotein(a), (g/l)			
Mean ± SD	0.189 ± 0.115	0.312 ± 0.300	<0.05#
Median	0.141	0.184	
Range	0.02 – 0.49	0.01 – 1.03	
Apolipoprotein A-I (g/l)	1.22 ± 0.21	1.11 ± 0.21	<0.05*
Apolipoprotein B (g/l)	0.71 ± 0.17	0.92 ± 0.20	<0.001*
Total cholesterol (mmol/l)	4.73 ± 0.88	4.96 ± 0.93	NS
Triacylglycerols (mmol/l)	1.51 ± 0.47	1.14 ± 0.37	<0.05*
HDL-cholesterol (mmol/l)	1.37 ± 0.18	1.19 ± 0.12	<0.001*
LDL-cholesterol (mmol/l)	2.78 ± 0.80	3.22 ± 0.88	<0.05*
Erythrocyte sedimentation rate (mm/h)	14.7 ± 1.6	32.5 ± 4.8	<0.01*
α_2-Globulins (%)	11.1 ± 1.8	13.6 ± 2.2	<0.01*
PMN Leukocytes (10^6/l)	3.1 ± 0.6	5.7 ± 1.0	<0.01*
PMN Leukocyte elastase (µg/l)	44 ± 19	244 ± 126	<0.001#

According to *Mann Whitney* U test * According to *Student*'s "t" test NS: Not significant

($p < 0.05$). Serum apolipoprotein A-I levels were significantly correlated with HDL-cholesterol levels in the patients ($r = 0.36$, $p < 0.05$). The mean serum apolipoprotein B level of the patients was significantly higher than that of the control group ($p < 0.001$). Also, triacylglycerols, HDL-cholesterol and LDL-cholesterol levels in the patients showed significant differences from those of the control group apart from total cholesterol levels. Other quantities related to the activity of disease in the patients were found to be significantly higher than those of control subjects (tab. 1). The quantities of the patients with thrombotic complications are shown in table 2. Lp(a) and other in these patients were found to be significantly different from the control subjects.

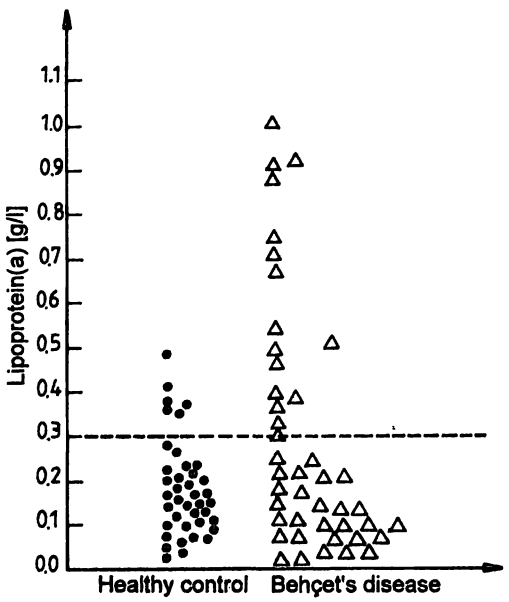

Fig. 1 Serum Lp(a) concentrations in patients with *Behçet*'s disease and in controls. (● shows controls and △ shows patients with *Behçet*'s disease, the dashed lines show the cut-off point for atherosclerosis).

Repeated measurements of the Lp(a) and other quantities were made in 10 patients while their disease was active or inactive (tab. 3). During the period of active disease, the mean concentration of Lp(a) was 0.326 g/l and a significantly decreased mean value of 0.250 g/l was obtained when the disease was inactive. Polymorphonuclear leukocytes, polymorphonuclear leukocyte elastase, α_2-globulins and erythrocyte sedimentation rate showed significant differences between the active and inactive periods of the disease ($p < 0.01$). Plasma concentrations of apolipoprotein A-I and HDL-cholesterol were lower, and apolipoprotein B concentration was higher when the disease was active (data not shown).

Discussion

Plasma Lp(a) levels, which are under genetic control, were highly skewed in the different ethnic groups. It has been reported that the mean Lp(a) value of the Turkish population (0.213 g/l) had a value near to the cut-off point (0.30 g/l) for atherosIcerosis (21). Also, *Behçet*'s disease is most common in the east part of the Mediterranean. The prevalence of the disease is reported to be 8/10 000 in Turkey (22). It is well known that high plasma Lp(a) level is associated with an increased incidence of cardiovascular and cerebrovascular disease because of its thrombogenic and atherogenic effects. On the endothelial surface, high plasma levels of Lp(a) can interfere with the process of plasminogen-plasmin conversion and result in decreased generation of plasmin and attenuation of clot lysis (23). Moreover, recent reports showed that Lp(a) has a direct action on endothelial function and induces the production of tissue plasminogen activator inhibitor by endothelium cells (24). Thus, high Lp(a) levels may have an association with

Tab. 2 Anthropometric and analytical quantities of the patients with thrombotic complications

Patients	Sex	Age	Lp(a)	PMN Leukocytes	Erythrocyte sedimentation rate	PMN Leukocyte elastase	α_2-Globulin
		(a)	(g/l)	(10^9/l)	(mm/h)	(µg/l)	(%)
E. V.	♂	27	1.03	5.7	40	320	13.4
Y. K.	♂	37	0.63	5.8	25	288	12.8
M. K.	♂	32	0.38	5.0	35	210	13.3
F. G.	♂	44	0.33	5.2	32	240	12.9
S. S.	♀	28	0.22	4.4	31	178	12.5
I. M:	♀	42	0.23	5.0	38	218	13.2
Mean			0.46**	5.2*	33.5*	242**	13.5*
Median			0.33	5.0	32.0	218	12.9
Range			0.22–1.03	4.4–5.7	25–40	178–320	12.5–13.4
Control Group							
Mean			0.18	3.1	14.7	44	11.1
Median			0.14	2.9	12.5	34	11.2
Range			0.02–0.55	1.8–4.6	7–25	21– 67	10.4–12.9

According to *Mann-Whitney* U test * $p < 0.05$, ** $p < 0.01$

Tab. 3 Concentration of Lp(a) and some acute phase reactants in patients in active and inactive periods in *Behçet*'s disease.

Patients	Lp(a) (g/l)		PMN Leukocytes (10^9/l)		Erythrocyte sedimentation rate (mm/h)		PMN Leukocyte elastase (µg/l)		α_2-Globulins (%)	
	active period	inactive period	active period	inactive period	active period	inactive period	active period	inactive period	active period	inactive period
1. Ü. Ş.	0.197	0.106	5.1	2.9	21	18	263	168	12.8	12.4
2. T. A.	0.124	0.082	4.7	3.1	32	21	198	110	13.4	12.6
3. S. K.	0.521	0.387	5.5	3.6	28	22	273	165	13.0	12.6
4. N. Ç.	0.138	0.092	4.9	2.6	26	20	235	167	12.8	12.2
5. Y. K.	0.637	0.551	5.8	3.1	25	19	288	140	12.8	12.3#
6. E. S.	0.121	0.057	4.7	2.5	26	16	180	120	13.1	12.4
7. A. K.	0.756	0.627	6.2	4.6	36	18	340	210	13.6	13.1
8. A. M.	0.151	0.143	4.7	2.5	40	27	160	110	13.6	13.1
9. M. K.	0.388	0.279	5.0	3.1	35	22	210	98	13.3	12.5#
10. İ. M.	0.235	0.207	5.8	3.2	32	18	250	124	13.2	12.7#
Median	0.216	0.174								
Mean	0.326	0.251	5.2	3.0	31	20	239	141	13.1	12.5
p* <	0.01		0.01		0.01		0.001		0.05	

* According to *Wilcoxon* test

\# The patients with thrombotic complications

decreased fibrinolysis and increased tendency to thrombosis. The basis of thrombotic risk of *Behçet*'s disease is not yet understood. On the other hand, it was reported that the reduced fibrinolytic activity caused by decreased production of tissue plasminogen activator and its increased production by endothelium due to vascular damage may contribute to thrombotic events in the patients (3, 6). The mean Lp(a) level (0.312 g/l) in patients with *Behçet*'s disease was found to be similar to the cut-off point. The mean Lp(a) level of the patients with thrombotic complications was found to be higher than that of the control group (tab. 2). We believe that the cutoff point of Lp(a) for atherogenesis differs in the various ethnic groups because of the many factors affecting atherogenesis (25) as well as the methodology and standardization problems of Lp(a) measurement. The thrombotic effect of Lp(a) via its apolipoprotein(a) part is dose-dependent because of competitive inhibition with plasminogen (11, 12). Therefore, Lp(a) may be more important for its thrombotic properties in *Behçet*'s disease since thrombotic events are more common than atherosclerosis in the disease. Sixteen subjects (35.5%) among the patients with *Behçet*'s disease had values higher than the cut-off point, and may therefore be at a much greater risk for thrombo-atherogenesis.

It has been previously reported that the thrombotic tendency and the abnormal fibrinolysis is related to the disease activity (6). Also, Lp(a) is known as an acute phase protein and is significantly correlated with acute phase reactants (13, 14). The change of plasma Lp(a) concentration was confirmed by the present study in patients with *Behçet*'s disease. Plasma Lp(a) levels in patients with inactive *Behçet*'s disease were found to be decreased by about 23% when compared to the active period of disease. The fluctuations of plasma Lp(a) levels with the activity of the disease may be a contributing risk factor for thrombogenesis in the active period of the disease. There is no effective lipid-lowering drug for Lp(a), the treatment of the active *Behçet*'s patients by appropriate drugs for *Behçet*'s disease may play an important role in lowering the plasma Lp(a) concentration.

Elastase is primarily located in the azurophil granules and is an active component of the phagocytic system of polymorphonuclear leukocytes (26, 27). Perivascular infiltration of polymorphonuclear leukocytes in *Behçet*'s patients is well known. High plasma polymorphonuclear leukocyte elastase levels, which are more specific than erythrocyte sedimentation rate and α_2-globulins, may represent the activity of vasculitis in patients (28). Positive correlations between plasma Lp(a) and polymorphonuclear leukocyte elastase indicate that effects of Lp(a) on development of thrombotic complications may be related to the activity of the disease. Moreover, Lp(a) has an independent effect on the decreased fibrinolysis in patients, and it is also associated with disturbed endothelial functions due to vasculitis.

The decreased concentrations of apolipoprotein A-I, HDL-cholesterol and triacylglycerols found in the patients agree with previous findings (29, 30). High apolipoprotein B levels in patients could be explained by the fact that apolipoprotein B presents chiefly in LDL and Lp(a).

In conclusion, we suggest that plasma Lp(a) concentrations be determined for patients with *Behçet*'s disease, and the patients with high Lp(a) levels be kept under close control, especially during the active period of the disease, and taken into remission as soon as possible.

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